REMARKS

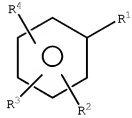
Claims 1, 15-18, and 21-25 have been amended in this Amendment A and Response After RCE. Specifically, claim 1 has been amended to further require the non-absorbent substrate to have an effective amount of a second active ingredient. Support for this amendment can be found in original dependent claim 14 and, further, in the instant Specification on page 12, paragraph [0031]. Additionally, claims 15-18 and 21-25 have been amended to be dependent upon claim 1. Claims 11 and 14 have been cancelled. Claims 1-4, 6-10, and 15-25 will be pending upon entry of this Amendment A and Response After RCE. Applicants respectfully request reconsideration and allowance of all pending claims.

1. Rejection of Claims 1-4 and 6-9 Under 35 U.S.C. §103(a)

Reconsideration is requested of the rejection of claims 1-4 and 6-9 under 35 U.S.C. §103(a) as being unpatentable over Robbins et al. (J. Clin. Microbiol. 1987) and Lambert (J. Applied Microbiol.) in view of D' Augustine et al. (U.S. 6,416,779) or D'Augustine et al. in view of Robbins et al. and Lambert.

Claim 1, as amended herein, is directed to an exoprotein inhibitor for inhibiting the production of exoproteins from Gram positive bacteria in and around a vagina. The exoprotein inhibitor comprises a **non-absorbent substrate for insertion into the vagina being selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a**

tampon applicator, and a douche. The non-absorbent substrate has deposited thereon an effective amount of a first active ingredient and **an effective amount of a second active ingredient.** The first active ingredient having the general formula:



wherein R^1 is $-OR^6OH$; R^6 is a divalent saturated or unsaturated aliphatic hydrocarbyl moiety; R^2, R^3, and R^4 are independently selected from the group consisting of H, OH, COOH, and $-C(O)R^9$; R^9 is hydrogen or a monovalent saturated or unsaturated aliphatic hydrocarbyl moiety. The second active ingredient having the general formula:

$$R^{10}—O—R^{11}$$

wherein R^{10} is a straight or branched alkyl or straight or branched alkenyl having from 8 to about 18 carbon atoms and R^{11} is selected from the group consisting of an alcohol, a polyalkoxylated sulfate salt and a polyalkoxylated sulfosuccinate salt. Both the first active ingredient and second active ingredient are effective in inhibiting the production of exoprotein from Gram positive bacteria.

Robbins et al. disclose an analysis of the influence of 17 commercially available tampons on the production of toxic shock syndrome toxin 1 (TSST-1) by *S. aureus* using a tampon disk method. Specifically, a disk containing 10-ml of agar medium

was overlaid with a Gelman GN-6 0.45-µm filter membrane and spread inoculated with 0.05 ml of an overnight still culture of *S. aureus* FRI-1169. In some samples, 10% blood was added to the agar medium. The test tampon was laid on the membrane and gently pressed down for uniform contact with the inoculated membrane. The disk was then sealed and incubated at 37°C for 19 hours. A plate count agar was used for enumeration of colonies in the tampon and membrane and a single gel diffusion tube method was used to determine the toxin content of the agar layer under the tampon and membrane. It was found that the amount of toxin produced increased with all tampons when blood was added to the agar medium, with an average of 42% over that without the addition of blood. Robbins et al. teach that one function of tampons may be to support the vaginal infection by supplying a fibrous surface for heavy colonization and to provide a sufficiently aerobic environment for toxin production.

Robbins et al. further disclose the effect of Aqualon, a surfactant, used alone or in combination with a deodorant in tampon manufacturing, on the growth and TSST-1 production by the *S. aureus*. It was found that while the Aqualon used alone on the tampon resulted in a decrease in CFU recovered from the tampon disk with a corresponding decrease in TSST-1 production associated with the disk, when blood was added to the agar, Aqualon showed little or **no effect on growth and TSST-1 production** by the *S. aureus* strain.[1] It was further shown, however, that when using the combined Aqualon and deodorant composition, there was a >50% decrease in the amount of TSST-1

[1] Robbins, et al. on page 1448.

recovered from both the agar layer and the tampon disk.[2]

Lambert discloses a method of examining the effect of inoculum size on the degree of inhibition observed with respect to inhibitor concentration. Specifically, the inoculum size dependencies of phenethyl alcohol, phenoxyethanol, *p*-chloro-*m*-cresol, trichloro-phenol, thymol, and dodecyltrimethylammonium bromide against *S. aureus* were analyzed. For all inhibitors examined, it was found that at lower inoculum levels, there was a greater biocidal effect, whereas at higher inoculum levels, there was a greater degree of quenching of the biocide, causing the inhibitor to act more as a simple (sublethal) inhibitor. As such, the method developed in Lambert may be used to quantify the effect in the region between reversible and irreversible damage, or sublethal injury to cell death. Furthermore, it was found in Lambert that phenethyl alcohol is a better inhibitor than phenoxyethanol against *S. aureus*.

Both Robbins et al. and Lambert fail to disclose the use of phenoxyethanol (or any compound having the structure of the first active ingredient as required in claim 1) **on a non-absorbent substrate being selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche for insertion into the vagina** for inhibiting exoproteins from Gram positive bacteria. Additionally, no where in Robbins et al. or Lambert is the use of a **second active ingredient** as further required in amended claim 1 on the non-absorbent substrate disclosed. Specifically, a second active ingredient having the structure as required in claim 1 was never even mentioned in the cited references. In an

[2] Id. at page 1449.

attempt to find each and every element of claim 1 as required by the M.P.E.P. for a determination of *prima facie* obviousness, the Office cites the D'Augustine et al. reference for combination with Robbins et al. and Lambert.

D' Augustine et al. disclose devices, methods, and compositions for treating vaginal fungal, bacterial, viral, and parasitic infections by intravaginal or transvaginal administration of therapeutic and/or palliative antifungal, antibacterial, antiviral or parasiticidal drugs to the vagina or to the uterus. Specifically, a device such as a tampon, tampon-like device, vaginal ring, pessary, cervical cup, vaginal sponge, intravaginal tablet, or intravaginal suppository, delivers the drug, which can be in the form of a paste, cream, ointment, microcapsule, solution, powder, or gel having a sufficient thickness to maintain prolonged vaginal epithelium and mucosa contact. In one embodiment, the drug can be incorporated into a cream, lotion, foam, paste, ointment, or gel which can be applied to the vagina using an applicator.[3]

In order for the Office to show a *prima facie* case of obviousness, M.P.E.P. §2143 requires that the Office must meet three criteria: (1) the prior art references must teach or suggest all of the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and (3) there must be some reasonable expectation of success. An obviousness determination is not the result of a rigid formula disassociated from the

[3] D' Augustine et al. at column 18, lines 24-26.

consideration of the facts of the case. The common sense of those skilled in the art can demonstrate why some combinations would have been obvious where others would not. The Office has clearly failed to meet its burden under numbers (1) and (2) above, as the references, alone or in combination fail to teach or suggest each and every limitation of Applicants' claim 1, and further, there is no motivation or suggestion to combine the Robbins et al., Lambert, and D' Augustine et al. references to arrive at Applicants' claim 1.

Specifically, as noted above, neither Robbins et al. nor Lambert teach the use of phenoxyethanol **on a non-absorbent substrate** for inhibiting exoprotein production. Furthermore, neither Robbins et al. nor Lambert teach the use of **a second active ingredient** on the non-absorbent substrate. At best, Robbins et al. teach that the use of a combination of surfactant and deodorant during the manufacturing of a tampon may inhibit exoprotein production and growth of *S. aureus*. No where, however, is phenoxyethanol or the second active ingredient having the structure of claim 1 even mentioned. Furthermore, while Lambert does analyze phenoxyethanol as one of six inhibitors that may inhibit exoprotein production, Lambert fails to teach or suggest the use of a second active ingredient with the pheoxyethanol to inhibit exoprotein production. In particular, no second active ingredient, either having the structure as required in claim 1 or otherwise, is even mentioned in Lambert.

The D'Augustine et al. reference fails to overcome the above shortcomings. As noted above, D'Augustine et al. teach numerous antibacterial compositions for treating bacterial

infections of the vagina. As such, why would one skilled in the art pick phenoxyethanol (or any compound having the structure required of the first active ingredient of claim 1) for use alone or in combination with the second active ingredient of claim 1 over all of the other non-toxic, antibacterial compositions present in the art, particularly when D'Augustine et al. provide numerous suitable antibacterial compositions to use with their non-absorbent devices and do not point to any need for alternatives? D' Augustine et al. simply teach compositions that can be used as antibacterials to treat bacterial infections of the vagina and devices for delivering the compositions; and even provide several commercially acceptable antibacterial compositions. The D' Augustine et al. reference fails to provide a reason why one skilled in the art would choose another antibacterial over those listed in the D' Augustine et al. reference or disclosed elsewhere in the art. Moreover, if one was to choose an additional antibacterial composition to use with the non-absorbent devices of D'Augustine et al., why would one choose phenoxyethanol when Lambert specifically stated that phenethyl alcohol is a better inhibitor? And, even if one would choose phenoxyethanol (which, as noted above, Applicants state that one skilled in the art simply would and could not do so), no where in any of the references is the second active ingredient taught or suggested and, as such, one skilled in the art would simply have no reason to add the second active ingredient of claim 1 for use in combination with the phenoxyethanol.

Moreover, the common sense of one ordinarily skilled in the art would not have provided a reason to combine the cited

references to arrive at Applicant's exoprotein inhibitor comprising a first active ingredient and a second active ingredient having the structures as required in claim 1 deposited on a non-absorbent substrate. As noted above, D'Augustine teaches numerous antibacterial compositions for treating bacterial infections of the vagina. As such, why would one skilled in the art be motivated to add any additional antibacterial compositions, much less the first and second active ingredients as recited in Applicants' instant claim 1? Based on the teachings in D'Augustine, one simply would not and could not find the motivation to do so. Furthermore, even if one skilled in the art did add the first active ingredient of claim 1 based on the teachings of Lambert, there is nothing in the cited references to motivate one to also include a second active ingredient, much less the specific second active ingredient of claim 1. Moreover, why would one skilled in the art be motivated to add the second active ingredient of claim 1 when Lambert teaches that phenoxyethanol already inhibits the exoprotein production? Based on the teachings of the cited references, there is simply no motivation to combine the cited references to arrive at Applicants' instant claim 1.

Furthermore, the Examiner states at page 3 of the Office Action that "[i]n response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Applicants respectfully submit that the combination of the cited references has been addressed, and is discussed in detail above.

As none of the cited references disclose each and every limitation of Applicants' claim 1 and, further, there is no motivation or suggestion to combine the references to arrive at each and every limitation of claim 1, claim 1 is patentable over Robbins et al. and Lambert in view of D'Augustine et al.

Claims 2-4 and 6-9 depend directly or indirectly on claim 1. As such, claims 2-4 and 6-9 are patentable for the same reasons as claim 1 set forth above, as well as for the additional elements they require.

2. Rejection of Claims 1-4, 6-11, and 14-25 Under 35 U.S.C. §103(a)

Reconsideration is requested of the rejection of claims 1-4, 6-11, and 14-25 under 35 U.S.C. §103(a) as being unpatentable over Robbins et al. (J. Clin. Microbiol. 1987) and Lambert (J. Applied Microbiol.) in view of Syverson (U.S. 5,612,045) or Syverson in view of Robbins et al. and Lambert.

Claim 1 is discussed above.

Robbins et al. and Lambert are discussed above. As discussed above, neither Robbins et al. nor Lambert teach or suggest the use of a first active ingredient and a second active ingredient having the structures as required in claim 1 on a non-absorbent substrate selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche, for insertion into the vagina for inhibiting exoproteins from Gram positive bacteria. The Syverson reference does not overcome these deficiencies. Specifically, Syverson is merely directed to

absorbent articles, such as catamenial tampons, which include an effective amount of an ether compound to substantially inhibit the production of exotoxins by Gram positive bacteria. Significantly, nowhere in Syverson is a first active ingredient as set forth in claim 1 even mentioned, much less that such a compound has antimicrobial properties or is effective in inhibiting the production of exoprotein from Gram positive bacteria when deposited on a non-absorbent substrate selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche.

The Office has stated that Syverson teaches both absorbent articles and non-absorbent articles with *S. aureus* exoprotein inhibiting compounds. Applicants acknowledge that Syverson discloses absorbent articles such as catamenial tampons. However, a disclosure of absorbent articles in general, or catamenial tampons in particular, is not a disclosure of a non-absorbent substrate; particularly, it is not a disclosure of a non-absorbent substrate selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche. Applicants submit that one skilled in the art would readily understand that a catamenial tampon is **not** a non-absorbent substrate, as required by applicants' claim 1. Applicants note a tampon applicator is one of the non-absorbent substrates listed in claim 1, not the tampon itself as disclosed in Syverson.

As none of the cited references teach or suggest using the first active ingredient and second active ingredient having the

structures as set forth in claim 1 on a non-absorbent substrate selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche for insertion into the vagina for inhibiting exoproteins from Gram positive bacteria, claim 1 is patentable over the combination of Robbins et al., Lambert, and Syverson.

3. Rejection of Claims 1-4, 6-11, and 14-25 Under Non-Statutory Obviousness-type Double Patenting

Claims 1-4, 6-11, and 14-25 have been provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-6, 10-11, 16-31, 34-46, and 48-51 of copending Application No. 09/969,299 in view of Robbins et al. Application No. 09/969,299 has been abandoned (See Exhibit A), and as such, this rejection should be withdrawn as moot.

Conclusion

In view of the above, Applicants respectfully request favorable reconsideration and allowance of all pending claims. The Commissioner is hereby authorized to charge any fee deficiency in connection with this Amendment A and Response After RCE to Deposit Account Number 01-2384.

Respectfully Submitted,

/Christopher M. Goff/

Christopher M. Goff, Reg. No. 41,785
ARMSTRONG TEASDALE LLP
One Metropolitan Square, 26th Floor
St. Louis, Missouri 63102
314-621-5070

CMG/JMB/dhm
Via EFS